Clinical microbiological case: chronic disseminated candidiasis unresponsive to treatment

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Please refer to the article on pages 435–436 of this issue to view the questions to which these answers refer.

ANSWERS AND DISCUSSION

1. Splenectomy was performed on the 58th day of pyrexia, as the patient was clinically unresponsive to amphotericin B and the bulk of the remaining lesions were in the spleen (Figure 1). An immediate febrile response was obtained 24 h following splenectomy. Liposomal amphotericin was replaced with maintenance therapy of 6 mg/kg per day oral fluconazole post-splenectomy. Pathologic examination of the spleen revealed extensive candida abscesses (Figure 2). However, splenic tissue cultures remained negative, most probably due to the prolonged antifungal therapy. Liver transaminase levels gradually returned to normal, and abdominal CT following 2 months of fluconazole treatment revealed no further lesions and marked regression of the few remaining liver and kidney abscesses. Fluconazole treatment was continued for a total of 6 months. A CT scan at the end of this period showed complete resolution of the lesions. Following his distressing ordeal, the patient refused further consolidation chemotherapy, but he remains in complete remission in terms of both AML and CDC 12 months following the reinduction chemotherapy. Predominant involvement of the spleen with little or no involvement of the liver by candida abscesses has been previously described as a less typical presentation of CDC in patients with hematologic malignancies [1,2], and splenectomy had a beneficial effect in conjunction with antifungal therapy in some of these patients [1–3]. This case illustrates that splenectomy may have a role in a minority of patients who are unresponsive to antifungal treatment and have the bulk of their lesions in the spleen.
2. The most appropriate therapeutic regimens and endpoints of treatment for CDC are not yet adequately defined, as CDC is a relatively uncommon disease, and controlled trials are difficult to conduct. Historically, the usual therapy for CDC has been amphotericin B deoxycholate. There is general agreement on the treatment dose of $\geq$0.7 mg/kg per day for amphotericin B deoxycholate, and some investigators would use higher doses, up to 1.5 mg/kg per day, for unstable patients [4]. Previous studies reported total amphotericin B deoxycholate doses ranging from 1.6 to 4 g prior to determination of non-response and change of therapy [5–7]. However, in almost 50% of the cases, administration for periods of up to 6 months and up to a total dose of 6 g was still not adequate to stop the infection from progressing [6,7]. The clinical progress of the patient is important in the timing of change of therapy. The frequent failure of this therapy may be related to the pharmacokinetics of amphotericin B deoxycholate, as candida infection can persist in the liver despite adequate concentrations of the drug [8]. In addition, prolonged amphotericin B deoxycholate therapy can lead to considerable toxicity, especially renal [6,7]. The patient in this presentation had severe uncontrolled hypokalemia with amphotericin B deoxycholate, which was replaced with liposomal amphotericin B. Lipid formulations of amphotericin B are approved for second-line therapy of patients who are intolerant of, or refractory to, therapy with conventional amphotericin B. Walsh et al. suggested that this could be due to the failure of $\geq$500 mg amphotericin B, initial renal insufficiency (creatinine $\geq$2.5 mg/dL or creatinine clearance $<$25 mL/min), a significant rise in creatinine (to 2.5 mg/dL in adults or 1.5 mg/dL in children), or severe acute administration-related toxicity [9]. Lipid formulations of amphotericin B permit administration of the drug at much higher doses, and they are also targeted naturally to the liver and spleen, which promotes their selective interactions with the *Candida* membrane [10]. Both in vivo and clinical studies indicate that these compounds are less toxic than, but as effective as, amphotericin B [11,12]. Nevertheless, their high cost and the lack of randomized trials in proven invasive candidiasis limit their front-line use [13]. The optimal dose of these compounds for serious

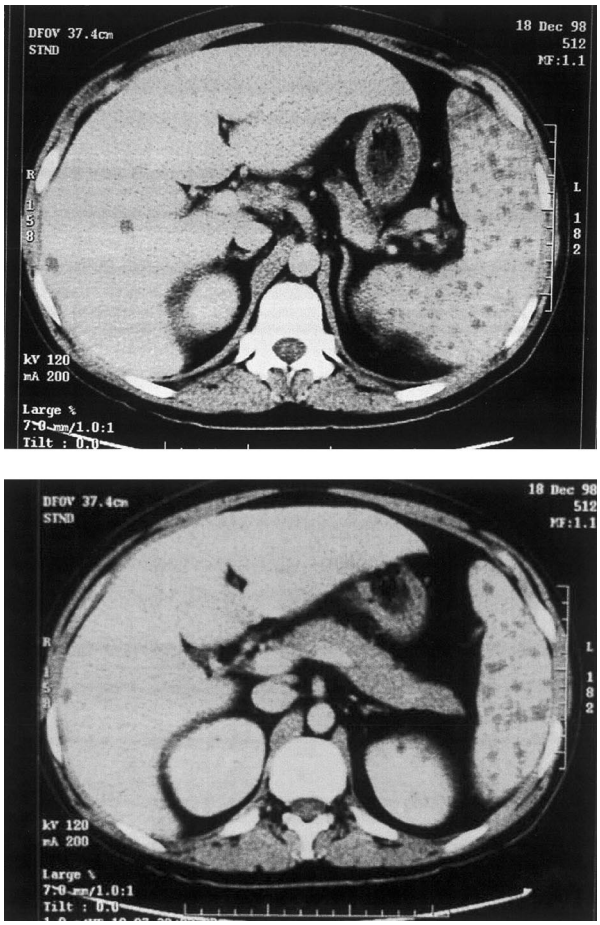

Figure 1 Abdominal CT scans showing numerous hypodense lesions within the spleen, and few lesions in the liver and kidney, consistent with abscesses.

Figure 2 Postsurgical dissection of the spleen demonstrating multiple candida abscesses.

candida infections is unclear, but 3–5 mg/kg appears to be suitable for most candidal infections [13].

3. Fluconazole, which is readily absorbed from the gastrointestinal tract and distributed widely in body tissues, including the liver, spleen and kidneys, has a response rate of about 80%, and is effective even among patients who failed to respond to previous amphotericin B treatment [6,14]. It is believed that fluconazole should be the drug of choice for CDC, because it is at least as effective as amphotericin B, is less toxic, can be given orally, and is less expensive than the lipid formulations of amphotericin B [4,15]. *C. albicans* is the causative agent in the majority of cases, but *C. krusei*, *C. tropicalis*, *C. glabrata* and other *Candida* species are increasingly responsible for invasive candidiasis [16]. *C. albicans* is commonly sensitive to fluconazole, but non-*albicans Candida* spp. may be resistant and require treatment with amphotericin B (particularly *C. krusei* and *C. glabrata*). Susceptibility of *Candida* to the available antifungal agents can be predicted if the species of the infecting isolate is known [16–18], but data correlating the clinical outcome of therapy with in vitro susceptibility are not precise [13]. Therapy in this case was initiated with fluconazole, but it was changed to amphotericin B deoxycholate following the isolation of non-*albicans Candida* species; esophageal cultures yielded *C. krusei*, known to be intrinsically resistant to fluconazole [19]. Fluconazole was recommenced post-splenectomy, as splenic tissue was assumed to be infected by the blood culture isolate *C. kefyr*, which is known to be sensitive to fluconazole as well as amphotericin B [20,21]. An oral dose of 6 mg/kg per day was chosen. Although dose-ranging studies for fluconazole have not been performed in patients with candidemia or deep candidal infections, most experts would initiate therapy at $\geq$6 mg/kg per day in stable patients who have not recently received azole therapy [13]. Duration of therapy should be highly individualized, and typically should be about 6 months [22].

In conclusion, Fluconazole is the treatment of choice for *C. albicans*, but treatment response is unknown for non-*albicans Candida* spp., which may require treatment with amphotericin B deoxycholate or a lipid formulation of amphotericin

B. Splenectomy has a role in a minority of patients who are unresponsive to antifungal treatment and have the bulk of their lesions in the spleen.

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